

## APPENDIX A

### WATER PATHWAY

General guidance for evaluating dermal exposure at Superfund sites is provided in Risk Assessment Guidance for Superfund (RAGS), Human Health Evaluation Manual (HHEM), Part A (U.S. EPA, 1989a). *Dermal Exposure Assessment Principles and Applications (DEA)* (U.S. EPA, 1992a) details procedures for estimating permeability coefficients of toxic chemicals and for evaluating the dermal absorbed dose. Section A.1 summarizes equations to evaluate the absorbed dose per event ( $DA_{\text{event}}$ ) in Equations 3.2 and 3.3 and other equations from the *DEA*. It also updates the regression model to predict the water permeability coefficient for organics. Statistical analysis of the regression equation provides the range of octanol/water partition coefficients ( $K_{ow}$ ) and molecular weights (MW) where this regression model could be used to predict permeability coefficients (Effective Prediction Domain - EPD), as recommended by the Science Advisory Board review in August 1992. Predictive values of the dermal permeability coefficient ( $K_p$ ) for over 200 compounds are provided with the 95% lower and upper confidence level in Appendix B (Exhibit B-2).

For chemicals with MW and  $K_{ow}$  outside the EPD, a model for predicting the fraction absorbed dose (FA) is proposed for those chemicals with high  $K_{ow}$ , taking into account the balance between the increased lag time of these chemicals in the stratum corneum and the desquamation of the skin during the absorption process; the consequence of which results in a net decrease in total systemic absorption.

Because the variability between the predicted and measured  $K_p$  values is no greater than the variability in interlaboratory replicated measurements, this guidance recommends the use of predicted  $K_p$  for all organic chemicals. This approach will ensure consistency between Agency risk assessments in estimating the dermal absorbed dose from water exposures. The Flynn database contains mostly hydrocarbons which might bear little resemblance to the typical compounds detected at Superfund sites. Predicting  $K_p$  from this correlation is uncertain for highly lipophilic and halogenated chemicals with log  $K_{ow}$  and MW values which are very high or low as compared to compounds in the Flynn database, as well as compounds for those chemicals which are partially or completely ionized. Alternative approaches are recommended for the highly lipophilic and halogenated chemicals, which attempt to reduce the uncertainty in their predicted  $K_p$ . Complete calculation of dermal absorbed dose (DAD) for the showering scenario using default assumptions is performed for over 200 compounds, and included in Appendix B (Exhibit B-3). For inorganics, Section A.2 provides permeability

coefficients of several metals. Section A.3 discusses the uncertainty of the parameters used in the estimation of the dermal dose. Section A.4 provides the assumptions and calculations for the screening provided in Chapter 2: Hazard Identification. Section A.5 summarizes the calculation procedures as well as the instructions for using the spreadsheets, which are provided on the Internet at the following URL:

<http://www.epa.gov/superfund/programs/risk/ragse/index.htm>

## A.1 DERMAL ABSORPTION OF ORGANIC COMPOUNDS

### A.1.1 ESTIMATION OF $K_p$ FOR ORGANIC COMPOUNDS

As discussed in *DEA*, the thin outermost layer of skin, the stratum corneum, is considered to be the main barrier to percutaneous absorption of most chemicals. The stratum corneum can be described as sheets of dead, flattened cells containing the protein keratin, held together by a lipoidal substance. Numerous studies, presented in the *DEA*, show that when this stratum corneum serves as the limiting barrier to diffusion through the skin, the permeability coefficient of a compound in water through the skin can be expressed as a function of its oil/water partition coefficient ( $K_{ow}$ , or most often,  $\log K_{ow}$ ), and its molecular weight (MW). This correlation was presented in the *DEA* as the Potts and Guy's equation (*DEA*: Equation 5.8), obtained based on the Flynn database (Flynn, 1991), shown in Exhibit B-1 of Appendix B.

In RAGS Part E, the Potts and Guy correlation has been refined to the following equation by excluding the three *in vivo* experimental data points in *DEA*, Table 5-8: ethyl benzene, styrene, and xylene, to limit the Flynn database to *in vitro* studies using human skin. The new algorithm results in Equation 3.8.

$$\log K_p = -2.80 + 0.66 \log K_{ow} - 0.0056 MW \quad (r^2 = 0.66) \quad (3.8)$$

where:

| Parameter | Definition (units)   | Default Value                     |
|-----------|--|-----------------------------------|
| $K_p$     | = Dermal permeability coefficient of compound in water (cm/hr) | Chemical-specific, see Appendix B |
| $K_{ow}$  | = Octanol/water partition coefficient (dimensionless)          | Chemical-specific, see Appendix B |
| MW        | = Molecular weight (g/mole)                                    | Chemical-specific, see Appendix B |

As can be seen from Equation 3.8, the molecular weight and polarity described by the octanol/water partition coefficient are the sole predictors of  $K_p$ . The above equation containing predicted values of  $K_p$  was evaluated against actual experimentally determined values for  $K_p$  and was found to correlate reasonably well, with few exceptions that may be attributed to experimental or analytical error. In *DEA*, it was recommended that the predicted values be used over the experimental measurements for the following two reasons: 1) for consistency with chemicals without an experimental measurement of  $K_p$  and, 2) to minimize inter-laboratory differences. Recently, Vecchia (1997) examined almost twice as many permeability coefficient values as those in the Flynn data set and found that replicated experimental measurements often vary by one to two orders of magnitude. This finding confirms the current continued recommendation that, for organics in water, the predicted values for  $K_p$  obtained from the above algorithm be used instead of actual measured values.

To determine the range of MW and  $\log K_{ow}$ , where Equation 3.8 would be valid for extrapolation to other chemicals given that the physico-chemical properties used in the  $K_p$  correlation (MW and  $\log K_{ow}$ ) are not completely independent of each other, the following Effective Prediction Domain (EPD) is determined using Mandel's approach (Mandel, 1982, 1985) for collinear data. This approach uses experimental data points in the derivation of the regression equation (here, the Flynn database, presented in Exhibit B-1) to determine the specific ranges of MW and  $\log K_{ow}$ , where the predictive power of the regression equation would be valid. This analysis uses the software MLAB (Civilized Software, Bethesda, MD, 1996).

Using Mandel's analysis (Mandel, 1985), the following boundaries of MW and  $\log K_{ow}$  for the above regression correlation were determined and are presented by Equations 3.9 and 3.10.

$$-0.06831 \leq 0.5103 \times 10^{-4} MW + 0.05616 \log K_{ow} \leq 0.5577 \quad (3.9)$$

$$-0.3010 \leq -0.5103 \times 10^{-4} MW + 0.05616 \log K_{ow} \leq 0.1758 \quad (3.10)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>                                | <u>Default Value</u>              |
|------------------|--|-----------------------------------|
| $K_{ow}$         | = Octanol/water partition coefficient<br>(dimensionless) | Chemical-specific, see Appendix B |
| MW               | = Molecular weight                                       | Chemical-specific, see Appendix B |

The points defining the EPD are shown in Exhibit A-1. The axes shown in the middle of the exhibit are obtained by translating the original axes (defined at 0 for both MW and  $\log K_{ow}$ ) to the center of the Flynn data set. The actual boundaries of the EPD are constructed by rotating these axes by 45°, then by drawing lines through the EPD points parallel to the new axes. All of Flynn's data would fall within the EPD, using the above exact solutions given by Equations 3.9 and 3.10.

From the list of 200 common pollutants, those which are outside the EPD, as defined by Equations 3.9 and 3.10, are summarized in Exhibit A-2. The compound characteristics for which the modified Potts and Guy correlation would not apply would be those with a combination of  $\log K_{ow}$  and MW satisfying those two equations.

The permeability coefficients of two classes of chemicals with very low  $K_{ow}$  and very high  $K_{ow}$  have been known not to correlate well with the  $\log K_{ow}$  (Leahy, 1990). Correlations like those in Equation 3.8 are based on the assumption that chemical absorption is primarily through a dissolution-diffusion process in the lipid material of the stratum corneum. Chemicals with low  $K_{ow}$  will have limited permeability through the lipid material of the stratum corneum, and penetration by other routes (e.g., appendages such as sweat glands or hair follicles or through regions of the stratum corneum with even minor damage) may contribute significantly. Permeability

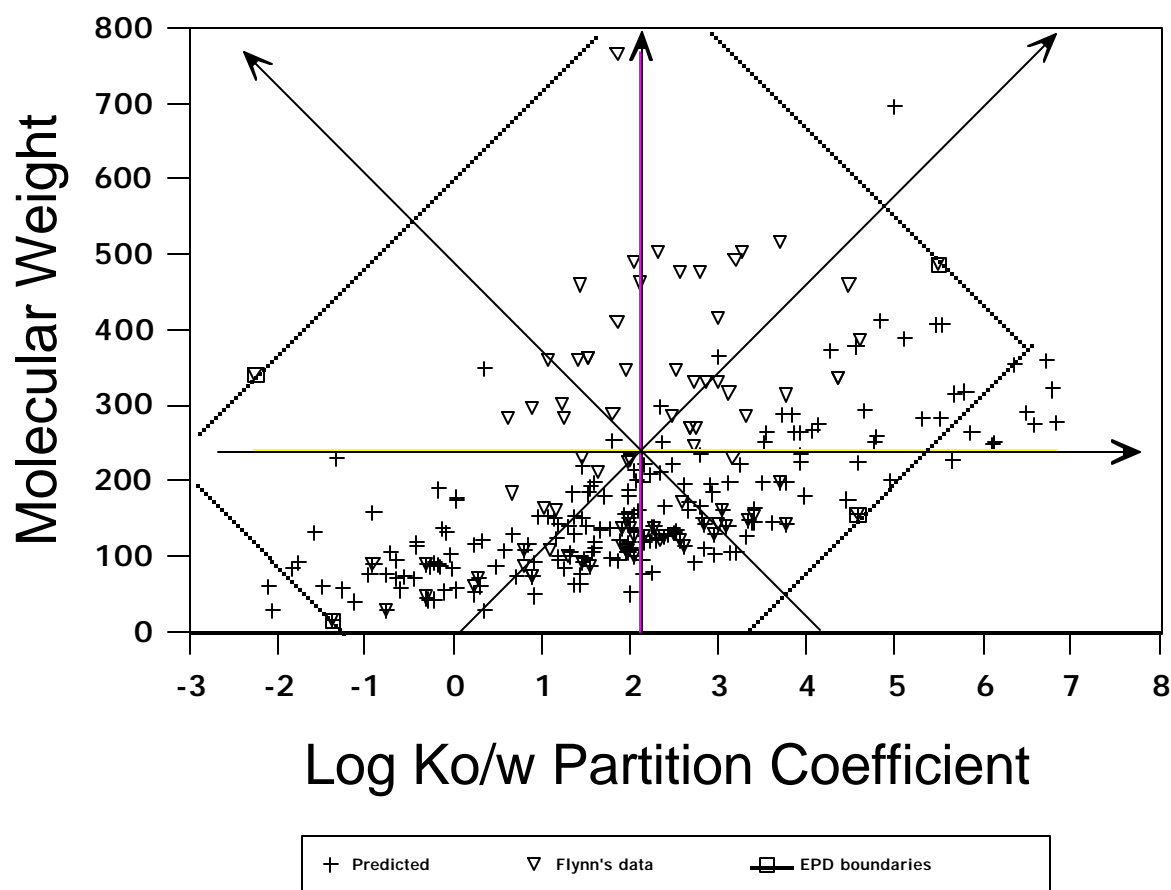
coefficients reported in the Flynn data set are measured at steady-state (i.e.,  $t_{\text{event}} > 2.4 J_{\text{event}}$ ). Consequently, for chemicals with very high  $\log K_{\text{ow}}$ , experimental values of permeability coefficients will include contributions of the viable epidermis.

Exhibit B-2 summarizes the predicted  $K_p$  for over 200 organic chemicals. Results of the current EPD analysis points out that for about 10% of those chemicals, this prediction would not be valid, according to the current use of Flynn's data set as the basis for the correlation equation between  $K_p$  and  $\log K_{\text{ow}}$  and MW. Strictly, chemicals with very large and very small  $K_{\text{ow}}$  are outside of the EPD of Equation 3.8. Although large variances in some data points contributed to the definition of the EPD, it is defined primarily by the properties of the data used to develop Equation 3.8. With no other data presently available for chemicals with very large and very small  $K_{\text{ow}}$ , it is appropriate to use Equation 3.8 as a preliminary estimate of  $K_p$ .

EXHIBIT A-1

# Effective Prediction Domain (EPD)

Boundaries for Kp estimation



**EXHIBIT A-2****COMPOUNDS FROM APPENDIX B WITH PERMEABILITY COEFFICIENTS OUTSIDE OF THE EFFECTIVE PREDICTION DOMAIN OF THE MODIFIED POTTS AND GUY CORRELATION**

| Log $K_{ow}$ < -2   |              |    | Log $K_{ow}$ > 4                  |              |       |
|---------------------|--------------|----|-----------------------------------|--------------|-------|
| Chemicals           | Log $K_{ow}$ | MW | Chemicals                         | Log $K_{ow}$ | MW    |
| Urea                | -2.11        | 60 | Benzo-a-anthracene                | 5.66         | 228   |
| Hydrazine H-sulfate | -2.07        | 32 | Benzo-a-pyrene                    | 6.10         | 250   |
|                     |              |    | Benzo-b-fluoranthene              | 6.12         | 252   |
|                     |              |    | Chrysene                          | 5.66         | 228   |
|                     |              |    | DDT                               | 6.36         | 355   |
|                     |              |    | Dibenzo(a,h)anthracene            | 6.84         | 278   |
|                     |              |    | Indeno(1,2,3-c,d)pyrene           | 6.58         | 276.3 |
|                     |              |    | PCB-chlorobiphenyl                | 6.50         | 292   |
|                     |              |    | PCB-hexachlorobiphenyl            | 6.72         | 361   |
|                     |              |    | Penanthrene                       | 4.46         | 178.2 |
|                     |              |    | Pentachlorophenol                 | 5.86         | 266   |
|                     |              |    | TCDD                              | 6.80         | 322   |
|                     |              |    | Tris(2,3-dibromopropyl) phosphate | 4.98         | 697.6 |

<sup>1</sup>Range was approximated from properties of the chemicals identified by the EPD analysis, but do not define the EPD.

**A.1.2 CALCULATION OF OTHER PARAMETERS IN  $DA_{event}$** 

The two-compartment model used to represent the skin (recommended in *DEA*) is unchanged in RAGS Part E, although all equations used in the evaluation of the dermal absorbed dose ( $DA_{event}$ ) are updated, according to the latest literature [Cleek and Bunge (1993) and Bunge and Cleek (1995)]. At short exposure durations, Equation 3.2 specifies that the  $DA_{event}$  is proportional to the stratum corneum permeability coefficient ( $K_p$ ) and the contribution of the permeability of the viable epidermis is not included. Significantly, B (the ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis) does not appear in the equation for short exposure duration [Eq 3.2] because the absorbing chemical has not had enough time to travel across the stratum corneum. Consequently, for short exposure durations, the amount of chemical absorbed depends only on the permeability coefficient ( $K_p$ ) of the stratum corneum (SC), the outermost skin layer. For longer exposure durations, Equation 3.3 specifies that the  $DA_{event}$  is restricted by the permeability of the viable epidermis and the stratum corneum, and thus B, the ratio of the permeability of the stratum corneum to that of the epidermis, appears in Equation 3.3.

The following presentation and Equations A.1 to A.8 summarize and update the equations from those in the *DEA*, Chapters 4 and 5, for estimating all parameters needed to evaluate  $DA_{event}$ . For a detailed explanation and derivation of the equations, please refer to *DEA*, Chapters 4 and 5, and Cleek and Bunge (1993) and Bunge and Cleek (1995).

The dimensionless parameter B expresses the relative contribution of the permeability coefficient of the compound in the stratum corneum ( $K_p$ , estimated from Equation 3.8) and its permeability coefficient in the viable epidermis. Bunge and Cleek (1995) discussed four different methods to estimate B, and recommended the use of Equation A.1, as adopted in this document.

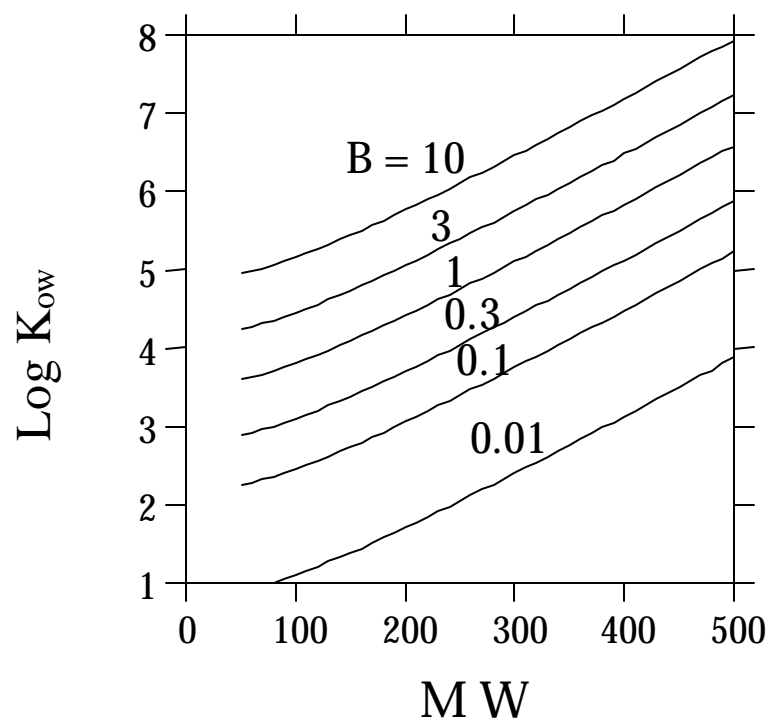
The complete derivation of Equation A.1 is presented in Bunge and Cleek (1995). As defined, B is a function of the permeability coefficient ( $K_p$ ), which is a function of molecular weight (MW) and the partition coefficient ( $\log K_{ow}$ ) given by Equation 3.8. Exhibit A-3 shows how B changes with MW and  $\log K_{ow}$ .

$$B = \frac{K_p}{K_{p,ve}} = K_p \frac{\sqrt{MW}}{2.6} \text{ cm/hr} \quad (\text{A.1})$$

where:

| <u>Parameter</u>  | <u>Definition (units)</u>   | <u>Default Value</u>   |
|-------------------|---|--|
| B                 | = Dimensionless ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis (ve) | --   |
| K <sub>p,ve</sub> | = Steady-state permeability coefficient through the viable epidermis (ve) (cm/hr)   | K <sub>p,ve</sub> = K <sub>ew</sub> D <sub>e</sub> /L <sub>e</sub> , K <sub>ew</sub> = 1 assuming epidermis behaves essentially as water; L <sub>e</sub> = 10 <sup>-2</sup> cm,<br>D <sub>e</sub> = 7.1 × 10 <sup>-6</sup> /MW cm <sup>2</sup> /s assuming D <sub>e</sub> = 10 <sup>-6</sup> cm <sup>2</sup> /s when MW = 50 (Bunge and Cleek, 1995) |
| K <sub>p</sub>    | = Dermal permeability coefficient in water (cm/hr)  | Equation 3.8   |
| MW                | = Molecular weight (g/mole)   | Chemical-specific  |
| K <sub>ew</sub>   | = Equilibrium partition coefficient between the epidermis and water for the absorbing chemical (dimensionless)  | Chemical-specific  |
| D <sub>e</sub>    | = Effective diffusivity of the absorbing chemical in the epidermis (cm <sup>2</sup> /hr)  | Chemical-specific  |
| L <sub>e</sub>    | = Effective thickness of the epidermis (cm)   | 10 <sup>-2</sup>   |

**EXHIBIT A-3**  
**EFFECTS OF MW AND LOG  $K_{ow}$  ON B**



Using the same approach as in *DEA*, Equations 5.13, A.2 and A.3 are derived to estimate  $D_{sc}/l_{sc}$  (cm/hr).

$$\log \frac{D_{sc}}{l_{sc}} = -2.80 - 0.0056 MW \quad (A.2)$$

or:

$$\frac{D_{sc}}{l_{sc}} = 10^{(-2.80 - 0.0056 MW)} \quad (A.3)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>   | <u>Default Value</u> |
|------------------|---|----------------------|
| $D_{sc}$         | = Effective diffusion coefficient for chemical transfer through the stratum corneum (cm <sup>2</sup> /hr) | Chemical-specific    |
| $l_{sc}$         | = Apparent thickness of stratum corneum (cm)  | 10 <sup>-3</sup> cm  |
| MW               | = Molecular weight (g/mole)   | Chemical-specific    |

Assuming  $l_{sc} = 10^{-3}$  cm as a default value for the thickness of the stratum corneum,  $\tau_{event}$  can be evaluated using Equation A.4:

$$\tau_{event} = \frac{l_{sc}^2}{6 D_{sc}} = 0.105 \times 10^{(0.0056 MW)} \quad (A.4)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>   | <u>Default Value</u> |
|------------------|---|----------------------|
| $J_{event}$      | = Lag time per event (hr/event)   | Chemical-specific    |
| $D_{sc}$         | = Effective diffusion coefficient for chemical transfer through the stratum corneum (cm <sup>2</sup> /hr) | Chemical-specific    |
| $l_{sc}$         | = Apparent thickness of stratum corneum (cm)  | 10 <sup>-3</sup>     |
| MW               | = Molecular weight (g/mole)   | Chemical-specific    |

Calculate  $t^*$ :

$$\text{If } B \leq 0.6, \text{ then } t^* = 2.4 \tau_{\text{event}} \quad (\text{A.5})$$

$$\text{If } B > 0.6, \text{ then } t^* = 6 \tau_{\text{event}} (b - \sqrt{b^2 - c^2}) \quad (\text{A.6})$$

$$b = \frac{2(1+B)^2}{\pi} - c \quad (\text{A.7})$$

$$c = \frac{1 + 3B + 3B^2}{3(1+B)} \quad (\text{A.8})$$

where:

| Parameter          | Definition (units)   | Default Value     |
|--------------------|--|-------------------|
| B                  | = Dimensionless ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis (ve) (dimensionless). | Chemical-specific |
| $t^*$              | = Time to reach steady-state (hr)  | Chemical-specific |
| $J_{\text{event}}$ | = Lag time per event (hr/event)  | Chemical-specific |
| $D_{\text{sc}}$    | = Effective diffusion coefficient for chemical transfer through the stratum corneum ( $\text{cm}^2/\text{hr}$ )  | Chemical-specific |
| $l_{\text{sc}}$    | = Apparent thickness of stratum corneum (cm)   | $10^{-3}$         |
| b, c               | = Correlation coefficients which have been fitted to the Flynn's data to give Equation 3.8   |                   |

All the above calculations are performed for over 200 chemicals for a defined default scenario (adults showering once a day for 35 minutes) with the results tabulated in Appendix B. These calculations are also provided in two Lotus spreadsheets: one for organics (ORG04\_01.WK4), and one for inorganics

(INORG04\_01.WK4), which will be available at the RAGS E website: <http://www.epa.gov/superfund/programs/risk/ragse/index.htm>.

### **A.1.3. MODEL ADJUSTMENT FOR LIPOPHILIC COMPOUNDS OUTSIDE EPD**

The above model assumes that all chemicals absorbed into the skin during the exposure event ( $t_{\text{event}}$ ) would eventually be absorbed into the systemic circulation, with the stratum corneum being the main barrier for most chemicals. For highly lipophilic chemicals, the viable epidermis can be a significant barrier for chemical transfer from the stratum corneum to the systemic circulation. When this occurs, the relative rate of desquamation of the stratum corneum and cell proliferation rate at the base of the viable epidermis contribute to a net decrease in the total amount of absorbed chemical. For similar reasons, stratum corneum desquamation can reduce the amount of absorption for chemicals that are not highly lipophilic but large enough (high MW) that penetration through the stratum corneum is slow (i.e., lag times are long).

A mathematical model was developed by Reddy *et al.* (2000) to account for the loss of chemical available for systemic absorption due to the desquamation of the outer layer of the stratum corneum. This model accounts for the relative rates of epidermal turnover and percutaneous penetration. Using the assumptions that the average turnover time of the stratum corneum is 14 days ( $t_{\text{sc}} \sim 14$  days or 336 hours), while that of the viable epidermis is 28 days (twice the time for the stratum corneum to turnover) in normal skin, Reddy *et al.* (2000) solved a set of partial differential mass balances for the stratum corneum and viable epidermis. After solving these equations, they calculated the fraction of the chemical that is ultimately absorbed (FA), allowing for losses by stratum corneum desquamation. Reddy *et al.* (2000) showed that FA is almost independent of  $t_{\text{event}}$ . However, FA depends strongly on the chemical's lipophilic characteristic and molecular weight as expressed in the B parameter and the lag time ( $\tau_{\text{event}}$ ), as illustrated in Exhibit A-4. A large number of the chemicals outside the EPD fall into this category, as well as a few chemicals within the EPD, especially those with high molecular weight. Given B and  $\tau_{\text{event}}$ , FA values can be obtained from Exhibit A-5. FAs are included in Exhibit B-3 and in the spreadsheet ORG04\_01.WK4. There are only a small number of chemicals that have a FA value  $< 0.5$ , but since most of those are highly lipophilic molecules that are often found in Superfund sites, the Dermal Workgroup is recommending that FA should be included in the calculation of DAD when applicable.

#### A.1.4 MODEL VALIDATION

Two papers in the literature have offered an attempt to validate the dermal absorption model (from now on referred to as the *DEA* model) presented in Section 3.1 for organics: McKone (1993) and Pirot *et al.* (1997).

McKone (1993) used experimentally measured and previously reported (Jo *et al.*, 1990) ratios of chloroform concentrations in inhaled air to tap-water concentration to evaluate the exposure model predictions. Particular attention was given to the implied dermal uptake measured by these experiments and to whether this is consistent with the recommended value for skin uptake of chloroform calculated by the *DEA* model. The Workgroup finds that the  $K_p$  implied by the Jo *et al.* (1990) shower data is 2.4 times higher than the value predicted by McKone and Howd (1992) and 6.7 times higher than the value predicted by the *DEA* model; and that the  $DA_{\text{event}}$  implied by the Jo *et al.* (1990) shower data is 2.6 times higher than the value predicted by McKone and Howd (1992) and 5 times higher than the value predicted by the *DEA* model. Also found was that both predictive models appear to have lag time estimates higher than is consistent with the Jo *et al.* (1990) shower data.

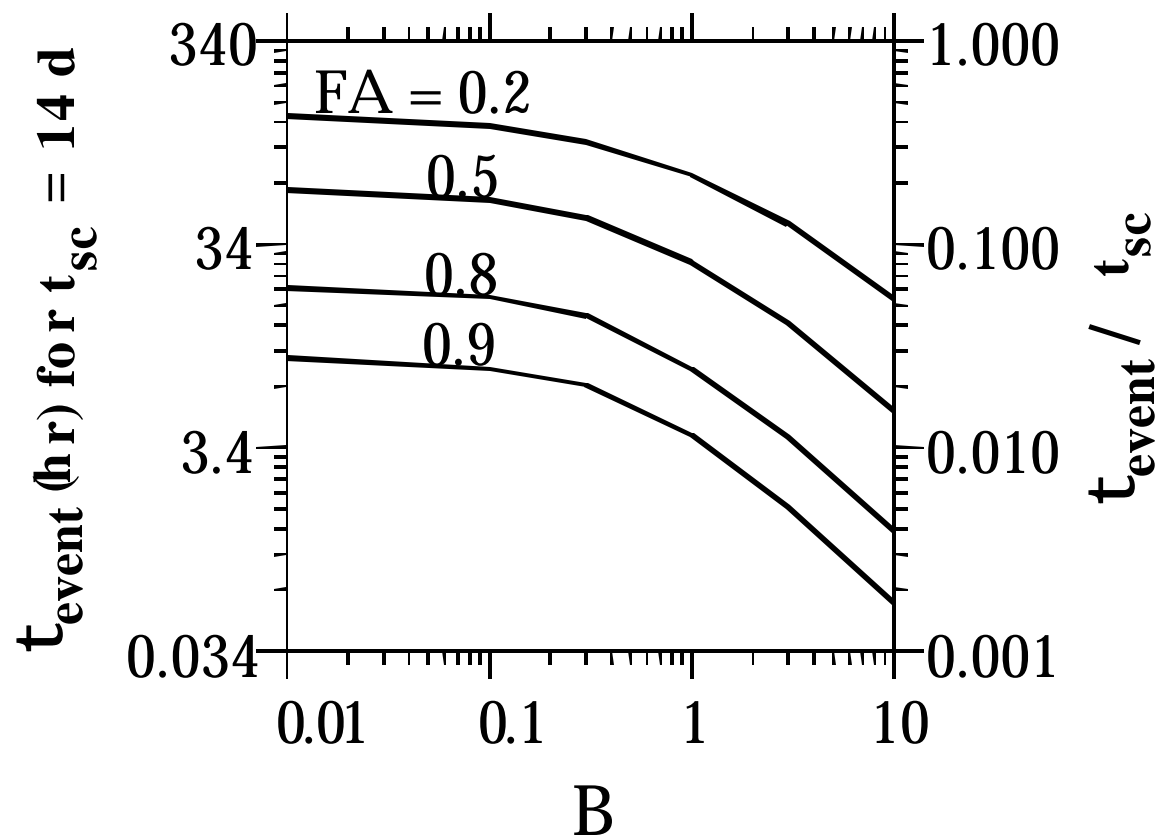
The Workgroup concludes that these results do not likely indicate any inherent flaws in the two predictive models, but instead reveal that models are only as reliable as the data they employ, and that a more formal process to assess sources of uncertainty is needed. For example, McKone and Howd (1992) have shown that the estimation error in their prediction of  $K_p$  has a geometric standard deviation (GSD) of three and they have estimated the GSD in the *DEA* model prediction of  $K_p$  as 3.8, confirmed as given by the 95% confidence level (95% CL) in Exhibit B-2. If this estimation error is applied to the measurement errors in the Jo *et al.* (1990a) experiments, the predicted and experimentally implied skin uptake parameters could reasonably differ from each other by factors of 3 to 7.

More recently, Pirot *et al.* (1997) have used attenuated total reflectance Fourier Transform infrared spectroscopy to quantify *in vivo* the uptake of 4-hydroxybenzonitrile by human stratum corneum. Results of this analysis were used to construct a time profile of the cumulative amount of 4-hydroxybenzonitrile permeating the skin as a function of time. The authors show that the calculated permeability coefficient ( $K_p \sim 3.6 \times 10^{-3}$  cm/hr) based on an assumed value of  $l_{sc} = 1.5 \times 10^{-2}$  cm, agrees well with that predicted by Equation 3.8, which yields a  $K_p = 6.8 \times 10^{-3}$  cm/hr.



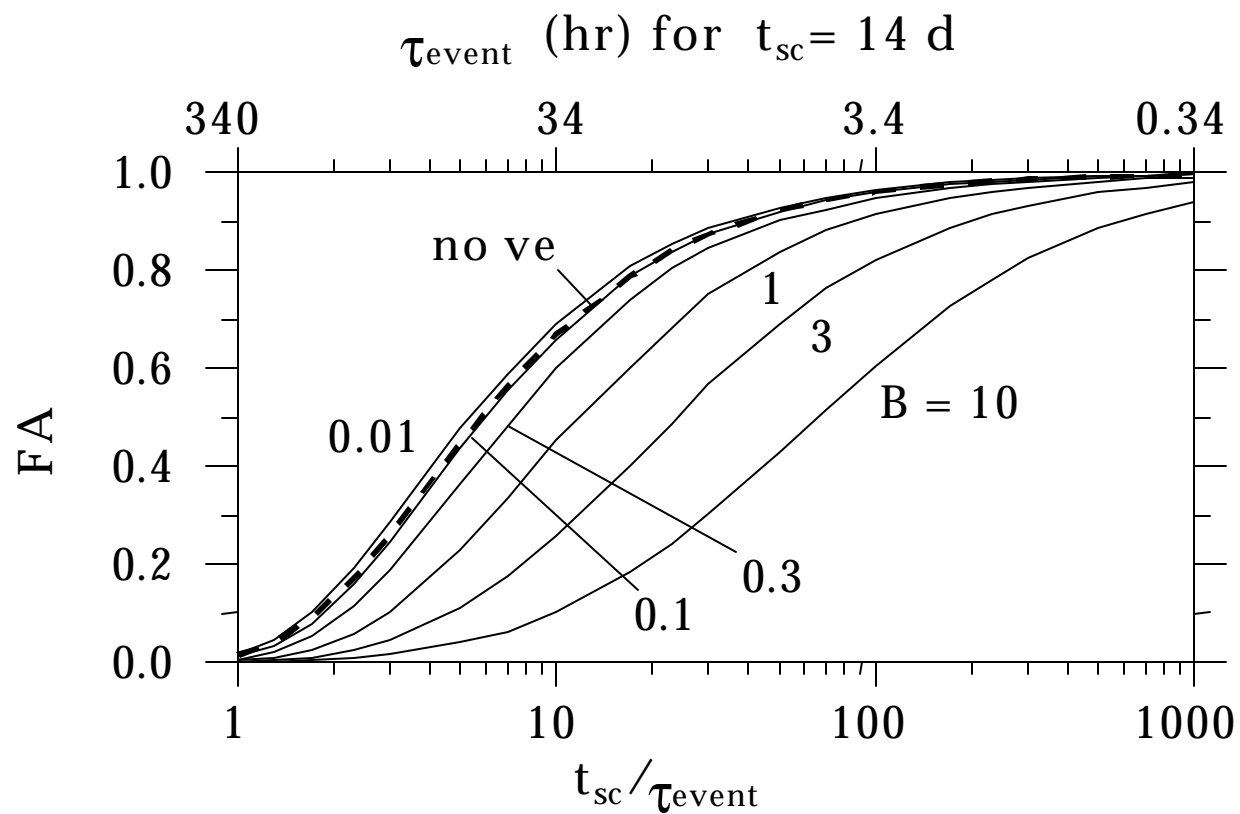
# EXHIBIT A-4

FRACTION ABSORBED (FA) AS A FUNCTION OF SPECIFIC COMBINATIONS OF B AND  $J_{\text{event}}/t_{\text{sc}}$



# EXHIBIT A-5

## EFFECT OF STRATUM CORNEUM TURNOVER ON FRACTION ABSORBED (WATER) AS A FUNCTION OF B



no ve: No viable epidermis—A model solution obtained assuming that the stratum corneum is the only barrier to dermal absorption.

## A.2 DERMAL ABSORPTION OF INORGANIC AND IONIZED ORGANIC COMPOUNDS

As discussed in Chapter 3, Equation 3.4 should be used in evaluating dermal absorbed dose for inorganics or highly ionized organic chemicals. As a consequence of and in keeping with recommendations in *DEA* (Chapter 5), using actual measured values of  $K_p$  is recommended for the inorganics. If no value is available, the permeability coefficient of  $1 \times 10^{-3}$  cm/hr is recommended as a default value (*DEA*) for all inorganics. Organometallics (e.g., tetraethyl lead) probably behave more like organic chemicals than inorganic chemicals and should be treated with the procedure outlined for organics.

### Dermal Absorbed Dose per event for Inorganic Compounds - Water Contact

$DA_{\text{event}}$  (mg/cm<sup>2</sup>-event) is calculated for inorganics or highly ionized organic chemicals as follows:

$$DA_{\text{event}} = K_p \times C_w \times t_{\text{event}} \quad (3.4)$$

where:

| Parameter           | Definition (units)   | Default Value                                     |
|---------------------|--|---|
| $DA_{\text{event}}$ | = Absorbed dose per event (mg/cm <sup>2</sup> -event)          | –   |
| $K_p$               | = Dermal permeability coefficient of compound in water (cm/hr) | Chemical-specific, see Exhibit A-6 and Appendix B |
| $C_w$               | = Chemical concentration in water (mg/cm <sup>3</sup> )        | Site-specific                                     |
| $t_{\text{event}}$  | = Event duration (hr/event)                                    | See Exhibit 3-2                                   |

Exhibit A-6 shows a more detailed compilation of the apparent permeability coefficients in humans for most of these inorganic chemicals at different concentrations (Hostynek *et al.*, 1998). The data in this table may be used to give a better estimate of the apparent permeability coefficients of the corresponding inorganic chemicals when the specific species is known. This table may also be useful in evaluating high exposure concentrations that approach those in several cited experimental studies.

**EXHIBIT A-6**  
**APPARENT PERMEABILITY COEFFICIENTS OF INORGANICS**

| Metal     | Compound                          | Concentration                    | Apparent Permeability Coefficient<br>$K_p$ (cm/hr) | Species and Experimental conditions     |
|-----------|-----------------------------------|----------------------------------|--|---|
| Cadmium   | $\text{CdCl}_2$                   | 0.239M                           | $1.1 \times 10^{-3}$                               | guinea pig, <i>in vivo</i> <sup>a</sup> |
| Chromium  | $\text{Na}_2\text{CrO}_4$         | 0.01-0.2 M                       | $1.0\text{-}2.1 \times 10^{-3}$                    | human, <i>in vivo</i>                   |
| Chromium  | $\text{Na}_2\text{CrO}_4$         | 0.017-0.398 M                    | $0.9\text{-}1.5 \times 10^{-3}$                    | human, <i>in vitro</i>                  |
| Chromium  | $\text{CrCl}_3$                   | 0.017-0.398 M                    | $1.0\text{-}1.4 \times 10^{-3}$                    | human, <i>in vitro</i>                  |
| Chromium  | $\text{Na}_2\text{CrO}_4$         | 0.034 M                          | $0.02\text{-}0.31 \times 10^{-3}$                  | human <i>in vitro</i> <sup>b</sup>      |
| Chromium  | $\text{K}_2\text{Cr}_2\text{O}_7$ | 0.03-0.25% Cr<br>(0.006-0.081 M) | $0.01\text{-}1.0 \times 10^{-3}$                   | human, <i>in vitro</i>                  |
| Chromium  | $\text{K}_2\text{Cr}_2\text{O}_7$ | 0.034 M Cr                       | $0.43 \times 10^{-3}$                              | human, <i>in vitro</i>                  |
| Chromium  | $\text{CrO}_4$                    | 0.005 M                          | $2.7 \times 10^{-3}$                               | human, <i>in vitro</i> <sup>c</sup>     |
| Chromium  | $\text{CrO}_4$                    | 2.1                              | $0.23 \times 10^{-3}$                              | human, <i>in vitro</i> <sup>c</sup>     |
| Chromium  | Cr(III)                           | 0.006 M                          | $0.4 \times 10^{-3}$                               | human, <i>in vitro</i> <sup>c</sup>     |
| Chromium  | Cr(III)                           | 1.2 M                            | $0.013 \times 10^{-3}$                             | human, <i>in vitro</i> <sup>c</sup>     |
| Chromium  | $\text{CrCl}_3$                   | 0.034 M                          | $0.041 \times 10^{-3}$                             | human, <i>in vitro</i>                  |
| Chromium  | $\text{Cr}(\text{NO}_3)_3$        | 0.034 M                          | $0.030 \times 10^{-3}$                             | human, <i>in vitro</i>                  |
| Mercury   | $\text{HgCl}_2$                   | 0.005 M                          | $0.02\text{-}0.88 \times 10^{-3}$                  | human, <i>in vitro</i> <sup>b</sup>     |
| Mercury   | $\text{HgCl}_2$                   | 0.080-0.239 M                    | $0.10\text{-}0.93 \times 10^{-3}$                  | human, <i>in vitro</i> <sup>b</sup>     |
| Mercury   | Hg vapor                          | 0.88-2.7 ng/m <sup>3</sup>       | $61.0\text{-}240.0 \times 10^{-3}$                 | human, <i>in vivo</i>                   |
| Potassium | KCl                               | 0.155 M                          | $2.0 \times 10^{-3}$                               | rabbit, <i>in vitro</i> <sup>d</sup>    |
| Potassium | KCl                               | 0.155 M                          | $2.0 \times 10^{-3}$                               | pig, <i>in vitro</i> <sup>e</sup>       |
| Nickel    | $\text{NiSO}_4$                   | 0.001-0.1 M                      | $0.003\text{-}0.01 \times 10^{-3}$                 | human, <i>in vitro</i>                  |
| Nickel    | $\text{NiSO}_4$                   | 0.001 M                          | $<0.002\text{-}0.27 \times 10^{-3}$                | human, <i>in vitro</i> <sup>f</sup>     |

**EXHIBIT A-6****APPARENT PERMEABILITY COEFFICIENTS OF INORGANICS** (continued)

| Metal  | Compound                              | Concentration           | Apparent Permeability Coefficient<br>$K_p$ (cm/hr)                             | Species and Experimental conditions |
|--------|---------------------------------------|-------------------------|--|-------------------------------------|
| Nickel | $\text{NiCl}_2$ , $\text{NiSO}_4$     | 1.32 mg Ni/ml           | $0.003\text{--}0.23 \times 10^{-3}$  | human, <i>in vitro</i>              |
| Nickel | $\text{NiCl}_2$                       | 0.62-5% $\text{NiCl}_2$ | $<0.0026\text{--}0.022 \times 10^{-3}$   | human, <i>in vitro</i>              |
| Nickel | $\text{NiCl}_2$                       | 5% $\text{NiCl}_2$      | $0.05 \times 10^{-3}$  | human, <i>in vitro</i>              |
| Lead   | $\text{Pb}(\text{CH}_3\text{CO}_2)_2$ | 6 mM, 9 mmol/kg         | $0.0005 \times 10^{-3}$  | human, <i>in vivo</i>               |
| Lead   | $\text{Pb}(\text{NO}_3)_2$            | 0.5 M                   | $0.13 \times 10^{-3}$  | human, <i>in vitro</i>              |
| Sodium | $\text{NaCl}$                         | 0.155 M                 | $0.06 \times 10^{-3}$  | human, <i>in vivo</i>               |
| Sodium | $\text{NaCl}$                         | 0.156 M                 | $0.028 \times 10^{-3}$ , fresh<br>$0.050 \times 10^{-3}$ , frozen<br>(medians) | human, <i>in vitro</i>              |
| Sodium | $\text{NaCl}$                         | 0.015-1.59 M            | $0.006\text{--}1.19 \times 10^{-3}$ (range)                                    | human, <i>in vitro</i>              |

-taken from Hostynek, *et al.*, 1998

<sup>a</sup>In guinea pigs; there are no published data on human skin.

<sup>b</sup>Depends upon the time interval; larger values are for the first few hours.

<sup>c</sup>Through epidermis.

<sup>d</sup>In rabbits; there are no published data with human skin.

<sup>e</sup>In pigs.

<sup>f</sup>From various vehicles and for various durations.

Recently, Vecchia (1997) collected permeability coefficients from the literature for *in vitro* penetration of human skin by several ionized chemicals, including cations, anions and zwitterions. Like permeability coefficients for inorganic chemicals, these  $K_p$  values are  $10^{-3}$  cm/hour or lower. Thus,  $10^{-3}$  cm/hour is recommended as a conservative estimate for ionized organic chemicals.

Calculations of DAD and screening levels for inorganics using default exposure assumptions are presented in Exhibit B-4 for all inorganics with a given experimental GI Absorption value ( $ABS_{GI}$  from Exhibit 4-1).

### A.3 UNCERTAINTY ANALYSIS

Sources of uncertainty in the above calculations compared with actual human exposure conditions include uncertainty in the model assumption, its formulation, and default values of the parameters used in models. Uncertainty discussion is provided below for the assumptions made in the development of the dermal absorption model, the modified Pott and Guy's  $K_p$  correlation, and the concentration of the chemicals in water.

As mentioned above, the skin is assumed to be a two-compartment model, with the two layers: stratum corneum and viable epidermis. Although exact solutions to this two-compartment model have been derived (Cleek and Bunge, 1993), these exact solutions are simplified in the recommended exposure assessment procedure for easy application for the regional risk assessors. Several assumptions are made with the application of these solutions, including the thickness of the stratum corneum ( $l_{sc} = 10^{-3}$  cm) and the use of part of Equation 3.8 in Equations A.2 and A.3 to estimate  $D_{sc}/l_{sc}$ .

For the permeability coefficient, the modified Flynn database is obtained from *in vitro* human diffusion studies, where the  $K_p$  was estimated. Vecchia (1997), in reexamining a more comprehensive database of  $K_p$  (twice the size of the Flynn database), found one to two orders of magnitude difference in replicated measurements. The correlation coefficient ( $r^2 = 0.67$ ) resulting from the modified Potts and Guy correlation shows that 67% of the experimentally observed variance in  $K_p$  is explained by this regression equation. The remaining 33% can be explained by inherent experimental errors and laboratory variabilities, and by the errors inherent in the choice of the  $K_{ow}$  value, whether it is measured or predicted. The residual error analysis provides

the average residual error between the measured  $\log K_p$  ( $K_{p\text{-msd}}$ ) and the  $\log K_p$  that is predicted ( $K_{p\text{-pred}}$ ) using the regression. The residual error or standard error of the estimator (SEE) is calculated in Equation A.9 as:

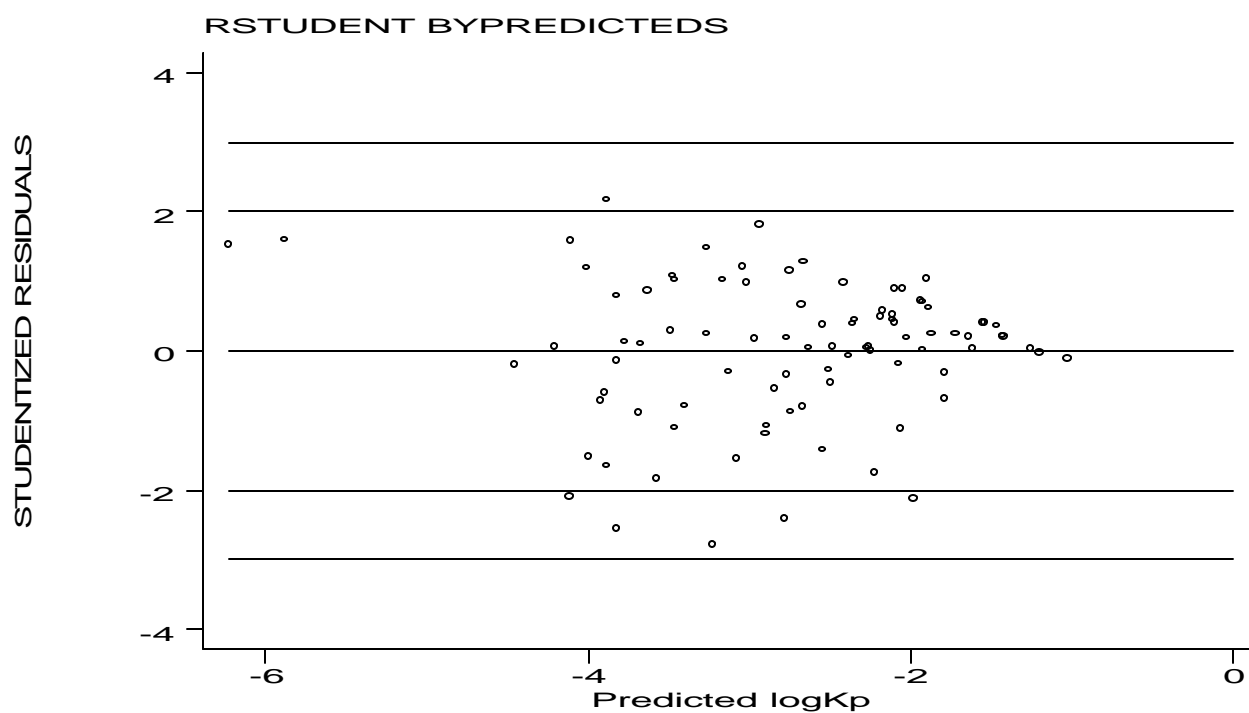
$$SEE \text{ of } \log K_p = \sqrt{\sum_{n=1}^N \frac{(\log K_{p\text{-msd}} - \log K_{p\text{-pred}})^2}{N-2}} \quad (\text{A.9})$$

where:

| <u>Parameter</u>    | <u>Definition (units)</u>                                      | <u>Default Value</u>                              |
|---------------------|--|---|
| N                   | = Number of chemical samples used in the estimation protocol   | Site-specific                                     |
| $K_p$               | = Dermal permeability coefficient of compound in water (cm/hr) | Chemical-specific, see Exhibit A-6 and Appendix B |
| $K_{p\text{-msd}}$  | = Measured $K_p$   | Chemical-specific                                 |
| $K_{p\text{-pred}}$ | = Predicted $K_p$  | Chemical-specific                                 |

where N is the number of chemical samples used in the estimation protocol, and  $\log K_{p\text{-msd}} - \log K_{p\text{-pred}}$  is the difference between logarithms of measured ( $K_{p\text{-msd}}$ ) and predicted values of  $K_p$  ( $K_{p\text{-pred}}$ ). For the Potts and Guy correlation, the SEE is calculated to be 0.69. Exhibit A-7 shows that there might be a wedge pattern to the residuals, which indicates the true value could be almost anything (i.e., large scatter between predicted and experimental value) when the predicted value is small. However, when the predicted  $K_p$  is large, the value is likely to be quite close to the true value. This result is consistent with experimental uncertainties, some of which are probably not chemically dependent (e.g., penetration through appendages or damaged regions of the skin). Consequently, these sources of variability contribute less significantly when the measured value is larger.

**EXHIBIT A-7**  
**STUDENTIZED RESIDUALS OF PREDICTED  $K_p$  VALUES**



The equations used for the estimation of the 95% confidence interval (lower and upper limits) are given in Equation A.10 as follows:

$$\text{95\% upper and lower confidence level of } K_p = K_p \pm t_{(1-\alpha/2, 1, 1-\alpha/2)} \sqrt{\text{Var}(K_p)} \quad (\text{A.10})$$

where:

|                          |   |  |
|--------------------------|---|--|
| $K_p$                    | = | Predicted $K_p$ from Equation 3.8  |
| $\text{Var}(K_p)$        | = | Variance of $K_p$ (see Draper and Smith, 1998 for definition of variance for linear regression with two independent variables)   |
| $\sqrt{\text{Var}(K_p)}$ | = | Standard error of the predicted $K_p$ . This standard error is smaller for compounds in the Flynn data set, which results only from errors in the correlation coefficients. For new compounds, this standard error is much larger because it includes both the errors from the correlation coefficients and the residual error of the model. |
| $t$                      | = | Student's $t$ distribution for two independent variables with a sample size of $n$ and a two-sided confidence interval of 100 (1-  |

as follows:

Wischut *et al.* (1995) provides an analysis of the reliability of five mathematical models used for simulating the permeability coefficient of substances through human skin. A database containing 123 measurements for 99 different chemicals was used in the analysis. Reliability of the models was evaluated by testing variation of regression coefficients and the residual variance for subsets of data, randomly selected from the complete database. This study found that a revised Potts and Guy model using these data had a lower residual variance than the McKone and Howd (1992) model, but that the McKone and Howd model and a revised unpublished model by Robinson (Proctor and Gamble) could provide better prediction of the permeability coefficient of highly lipophilic compounds. The Robinson model for  $K_p$  is based on a theoretical basis of a maximum permeability coefficient to account for the limiting transport properties of the epidermis. The current approach in this document, using the Potts and Guy model in combination with the parameter  $B$  in the dermal absorption model to account for the effect of permeation in the epidermis, provides the same theoretical basis as the Robinson model for  $K_p$  alone. Among all the models discussed by Wischut *et al.* (1995), the revised Robinson model had the lowest residual variance, which is the SEE squared.

Several other physico-chemical characteristics can also be added to improve the above correlation, e.g., molar volume (Potts and Guy, 1992). Alternatively, the data could be grouped into smaller subsets of more homogeneous chemical classes, which could yield much better correlations, as reviewed and summarized in *DEA*, Table 5.6. This selection of the Potts and Guy approach is based on the universal availability of the MW and the  $K_{ow}$ , which allow for the easy extrapolation of this correlation to other organic chemicals. However, the large uncertainty resulting from these assumptions gives a 95% confidence interval of one to three orders of magnitude for the  $K_p$  estimated by this correlation, as shown in Exhibits B-1 and B-2. Because of this uncertainty, suggestions have been made to simplify the skin two-compartment diffusion model to the standard Ficks' first law, which would provide a more conservative apparent  $K_p$ . This approach is retained to balance application of more defined, available modeling to limited empirical data correlation. This approach might not improve the uncertainty much for chemicals with small lag time, reflected by using the simplified Ficks' first law equation for the inorganics. However, for those chemicals with long lag time, the two-compartment approach, together with the empirically predicted  $K_p$ , provides a much better description of the dermal absorption processes.

A note of caution is added here regarding the use of Equation 3.8 to estimate  $K_p$  for halogenated and other chemicals with large MW relative to their molar volume. Notably, the list of 200 pollutants in Appendix B includes several halogenated chemicals. Specifically, correlations like Equation 3.8 would be expected to underestimate  $K_p$ . The Flynn data set, from which Equation 3.8 was derived, consists almost entirely of hydrocarbons with a relatively constant ratio of molar volume to MW. As a consequence, for this database, there is almost no statistical difference in a regression of the  $K_p$  data, using MW to represent molecular size compared with a regression using molar volume (the quantity which is expected to control permeability) to represent molecular size. Because halogenated chemicals have a lower ratio of molar volume relative to their MW than hydrocarbons (due to the relatively weighty halogen atom), the  $K_p$  correlation based on MW of hydrocarbons will tend to underestimate permeability coefficients for halogenated organic chemicals. Unfortunately,  $K_p$  data are only available for a small number of halogenated organic chemicals [only seven in the Vecchia (1997) database, which is larger than the Flynn data set]. Vecchia (1997) found that  $K_p$  values for six of seven halogenated compounds were underestimated by a correlation of similar form to Equation 3.8. To address this problem, a new  $K_p$  correlation based on molar volume and  $\log K_{ow}$  will be explored.

The EPD for the modified Potts and Guy correlation, an evaluation based on Mandel's approach, depends entirely upon the database used to generate both the correlation and the EPD. Sources of uncertainty in this Flynn database include actual chemicals used for the correlation, as well as values of  $K_{ow}$  associated with those

chemicals, values which would contribute to the predictability of the correlation, as well as to the range defined by the EPD. For compounds with long lag time, where the adjustment of the fraction absorbed (FA) takes into consideration the desquamation of the skin, another uncertainty of about 10-20% arises from the assumption of steady-state and the approximation of these values from Exhibit A-5.

For highly lipophilic molecules, which are often found on Superfund sites, there are uncertainties in several steps of this approach. The permeability coefficients ( $K_p$ ) of most of these compounds are outside of the predictive domain, and the large uncertainty of these values is reflected in the large range of the 95% confidence interval limit. For most of these chemicals, a value of  $FA < 1$  is due to the effects of desquamation. However, estimation of the Dermal/Oral contribution using standard default assumptions in Exhibit B-3 for these compounds reveals that even using the lower 95% confidence limit of the  $K_p$ , a few compounds would yield a ratio  $Dermal/Oral > 10\%$ , which is the criterion used for inclusion of these chemicals in the site risk assessment quantitative analysis. These results are shown in Exhibit A-8.

The recommendations from the Dermal Workgroup for these chemicals include: 1) conducting experimental studies to obtain their  $K_p$  values, for at least *in vitro* exposure conditions under saturation concentration, and 2) including these chemicals in the quantitative analysis and characterizing the uncertainty of the risk assessment results clearly.

For the concentrations of chemicals in water ( $C_w$ ) in Equations 3.2 through 3.4, values used for  $C_w$  should reflect the available concentration of the chemicals in water for dermal absorption, and might be potentially different from the measured field values. This difference would result from the conditions of the samples and the type of chemicals to be analyzed. For the sample conditions, higher concentration of chemicals of interest might be found in unfiltered groundwater samples as compared to filtered samples, due to the existence of particulate matter and undissolved chemicals. However, to be consistent with existing RAGS guidance (U.S. EPA, 1989), it is recommended that unfiltered samples be used as the basis for estimating the chemical concentration ( $C_w$ ) for calculating the dermal dose.

**EXHIBIT A-8****EVALUATION OF DERMAL/ORAL CONTRIBUTION FOR LIPOPHILIC COMPOUNDS**

|       | CHEMICAL                             | CAS No.  | MWT   | log<br>$K_{ow}$ | $K_p$<br>95% LCL | $K_p$<br>(cm/hr)<br>predicted | $K_p$<br>95% UCL | FA  | Derm/<br>Oral<br>95% LCL | Derm/<br>Oral<br>Average<br>K <sub>perage</sub> | Derm/<br>Oral<br>95%<br>UCL $K_p$ |
|-------|--------------------------------------|----------|-------|-----------------|------------------|-------------------------------|------------------|-----|--------------------------|---|-----------------------------------|
| * 19  | Benzo-a-anthracene                   | 56553    | 228.3 | 5.66            | 1.7E-02          | 4.7E-01                       | 1.3E+01          | 1   | 45%                      | 1283%   | 36172%                            |
| * 20  | Benzo-a-pyrene                       | 50328    | 250.0 | 6.10            | 2.4E-02          | 7.0E-01                       | 2.0E+01          | 1   | 75%                      | 2186%   | 63553%                            |
| * 21  | Benzo-b-fluoranthene                 | 205992   | 252.3 | 6.12            | 2.4E-02          | 7.0E-01                       | 2.0E+01          | 1   | 76%                      | 2221%   | 64633%                            |
| * 49  | Chrysene                             | 218019   | 228.3 | 5.66            | 1.7E-02          | 4.7E-01                       | 1.3E+01          | 1   | 45%                      | 1283%   | 36172%                            |
| * 56  | DDT                                  | 50293    | 355.0 | 6.36            | 9.2E-03          | 2.7E-01                       | 7.8E+00          | 0.7 | 40%                      | 1156%   | 33682%                            |
| * 62  | Dibenzo(a,h)anthracene               | 53703    | 278.4 | 6.84            | 4.9E-02          | 1.5E+00                       | 4.7E+01          | 0.6 | 110%                     | 3388%   | 104681%                           |
| * 126 | Indeno(1,2,3-CD)pyrene               | 193395   | 276.3 | 6.58            | 3.5E-02          | 1.0E+00                       | 3.1E+01          | 0.6 | 77%                      | 2307%   | 69550%                            |
| * 170 | PCB-chlorobiphenyl, 4-               | 2051629  | 292.0 | 6.50            | 2.5E-02          | 7.5E-01                       | 2.2E+01          | 0.6 | 62%                      | 1844%   | 54977%                            |
| * 171 | PCB-hexachlorobiphenyl               | 26601649 | 361.0 | 6.72            | 1.4E-02          | 4.3E-01                       | 1.3E+01          | 0.5 | 46%                      | 1376%   | 41414%                            |
| * 173 | Pentachlorophenol                    | 87865    | 266.4 | 5.86            | 1.4E-02          | 3.9E-01                       | 1.1E+01          | 0.9 | 43%                      | 1226%   | 34780%                            |
| * 176 | Phenanthrene                         | 85018    | 178.2 | 4.46            | 5.5E-03          | 1.4E-01                       | 3.8E+00          | 1   | 11%                      | 283%  | 7446%                             |
| * 186 | TCDD                                 | 1746016  | 322.0 | 6.80            | 2.7E-02          | 8.1E-01                       | 2.5E+01          | 0.5 | 66%                      | 2003%   | 61044%                            |
| * 203 | Tris(2,3-dibromopropyl)<br>phosphate | 126727   | 697.6 | 4.98            | 1.3E-05          | 3.9E-04                       | 1.1E-02          | 1   | 1%                       | 22%   | 642%                              |

Note: All the above calculations are done using the same assumptions as those in Exhibit B-3

The types of chemicals in the samples would also influence the available concentration of the chemicals for dermal absorption, due to their ionization status in the samples. This discussion is detailed in Bunge and McDougal (1998). For organic chemicals in which  $K_p$  is calculated using Equation 3.8,  $C_w$  should be the concentration of only the non-ionized fraction of the chemical,  $C_u$ , to be consistent. If the organic chemical is not ionizable,  $C_w$  is equal to the total concentration of chemical in the aqueous solution,  $C_{tot}$ . For organic acids with one dominant acid-base reaction of  $pK_a$ ,  $C_u$  is calculated using Equations A.11 or A.12.

For organic acids with one dominant acid-base reaction of  $pK_a$ ,  $C_u$  is:

$$C_u = \frac{C_{tot}}{1 + 10^{(pH - pK_a)}} \quad (A.11)$$

For organic bases with one dominant acid-base reaction:

$$C_u = \frac{C_{tot}}{1 + 10^{(pK_a - pH)}} \quad (A.12)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>  | <u>Default Value</u> |
|------------------|--|----------------------|
| $C_u$            | = Concentration of non-ionized species (mg/l)  | Site-specific        |
| $C_{tot}$        | = Total concentration (mg/l)   | Site-specific        |
| $pK_a$           | = Log of the ionization equilibrium constant of the chemical in the aqueous solution | Chemical-specific    |

For organic chemicals with more than one ionizable group, in general,  $pK_a$  values should be known for all ionizing reactions, and the concentration of the non-ionized species,  $C_u$ , should be calculated by combining expressions for species mass balances, electroneutrality, and reaction equilibrium.

For organic chemicals, both ionized and non-ionized species at conditions of the aqueous solution, calculate  $DA_{event}$  as the sum of the  $DA_{event}$  for the non-ionized species (using Equations 3.2 and 3.3 and the concentration of the non-ionized species,  $C_w = C_u$ , with the  $K_p$  of the non-ionized species) and the  $DA_{event}$  for the ionized species (using Equations 3.2 and 3.3 and the concentration of the ionized form of the chemical,  $C_w = C_{tot} - C_u$ , with the  $K_p$  of the ionized species). For inorganic chemicals,  $C_w = C_{tot}$ . If the  $K_p$  of the ionized species is always smaller than the  $K_p$  of the non-ionized species, using  $C_w$  as a default total concentration would always yield a conservative estimate of the dermal absorbed dose.

#### A.4 SCREENING PROCEDURE FOR CHEMICALS IN WATER

For purposes of scoping and planning an exposure and risk assessment, it is useful to know when it is important to consider dermal exposure pathways. Assessors must decide what level (from cursory to detailed) of

analysis is needed to make this decision. The following screening procedure addresses this issue primarily by analyzing when the dermal exposure route is likely to be significant when compared to the other routes of exposure. This discussion is based on methodology presented in Chapter 9 of the *DEA* using the parameters provided in this current guidance, and provides the basis for the current Chapter 2 on Hazard Identification. Readers are encouraged to consult the *DEA* document for more details.

The first step is to identify the chemicals of interest. The next step is to make a preliminary analysis of the chemical's environmental fate and the population behavior to judge whether dermal contact may occur. The third step is to review the dermal toxicity of the compound and determine if it can cause acute effects. The scope of this screening procedure has been limited to dermal exposure assessments in support of risk assessments for systemic chronic health effects. However, consideration of other types of health effects can be a critical factor in determining the overall importance of the dermal exposure route. Even if the amount of a compound contacting the skin is small compared to the amount ingested or inhaled, the dermal route can still be very important to consider for compounds that are acutely toxic to the skin.

The remainder of this procedure evaluates the importance of dermal contact by comparing it to other exposure routes that are likely to occur concurrently. For example, the importance of dermal contact with water is evaluated by assuming that the same water is used for drinking purposes as for swimming or bathing and comparing these two pathways. However, the underlying assumption that concurrent exposure routes will occur is not valid in all situations. For example, the water in a contaminated quarry may not be used as a domestic water supply but may be used for occasional recreational swimming. Even where concurrent exposure routes occur, the contaminant concentrations may differ. For example, in a situation involving a contaminated river used as a domestic water supply, swimmers may be exposed to a higher concentration in the river than occurs during ingestion of tap water due to treatment. Thus, the assessor should confirm the assumptions that concurrent exposures occur and that the same contaminant levels apply. Where these assumptions are not valid, dermal exposure should be evaluated independently.

Where the same water supply is used for drinking and bathing, the importance of dermal contact with water can be evaluated by comparing the possible absorbed dose occurring during bathing relative to that occurring as a result of ingestion, represented by the standard default of drinking 2 liters of water per day per person. Assuming a 35 min (0.58 hr) showering (RME value from Exhibit 3-2), for all the 200 pollutants included in Exhibit B-3, the following ratio of the dermal absorbed dose relative to ingestion is presented in Equations A.13

to A.16 for organics and Equation A.13 for inorganics.

$$\frac{\text{Dermal Dose}}{\text{Ingestion Dose}} = \frac{DA_{\text{event}}(SA)(EV)}{(C_w)(IR)(1000\text{cm}^3/\text{L})(ABS_{GI})} \quad (\text{A.13})$$

For short exposure ( $t_{\text{event}} < t^*$ ):

where:

$$\frac{\text{Dermal Dose}}{\text{Ingestion Dose}} = \frac{2(C_w)(FA)(K_p)(SA)(EV)\sqrt{\frac{6(t_{\text{event}} \times t_{\text{event}})}{1}}}{(C_w)(IR)(1000\text{cm}^3/\text{L})(ABS_{GI})} \quad (\text{A.14})$$

| Parameter           | Definition (units)   | Default values         |
|---------------------|--|------------------------|
| $DA_{\text{event}}$ | = Absorbed dose per event (mg/cm <sup>2</sup> -event)                            | Equation 3.2           |
| $C_w$               | = Chemical concentration in water (mg/cm <sup>3</sup> )                          | 1 mg/l or 1 ppm        |
| FA                  | = Fraction absorbed (dimensionless)  | Exhibit A-5            |
| $K_p$               | = Dermal permeability coefficient of compound in water (cm/hour)                 | Equation 3.8           |
| $J_{\text{event}}$  | = Lag time per event (hr/event)  | Equation A.4           |
| $t_{\text{event}}$  | = Event duration (hr/event)  | 35 minutes             |
| SA                  | = Skin surface area available for contact (cm <sup>2</sup> )                     | 18,000 cm <sup>2</sup> |
| EV                  | = Event frequency (events/day)   | 1 event/day            |
| IR                  | = Water ingestion rate (L/day)   | 2 L/day                |
| $ABS_{GI}$          | = Fraction of contaminant absorbed in the gastrointestinal tract (dimensionless) | 1                      |
| $t^*$               | = Time to reach steady-state (hr)  | Chemical-specific      |

Assuming an adult ingestion rate (IR) of 2 L/day, GI tract absorption fraction ( $ABS_{GI}$ ) of 1, a skin area of 18,000 cm<sup>2</sup>, and several other factors (Equation A.13 and A.14), this ratio becomes:

$$\frac{\text{Dermal Dose}}{\text{Ingested Dose}} = 19 \text{ FA } K_p \sqrt{\tau_{\text{event}}} \quad (\text{A.15})$$

where:

| Parameter          | Definition (units)   | Default Value                     |
|--------------------|--|-----------------------------------|
| $K_p$              | = Dermal permeability coefficient of compound in water (cm/hour) | Chemical-specific, see Appendix B |
| $J_{\text{event}}$ | = Lag time per event (hr/event)                                  | Chemical-specific, see Appendix B |
| FA                 | = Fraction absorbed (dimensionless)                              | Chemical-specific, see Appendix B |

Using the screening criteria of 10% dermal to ingestion, the dermal dose exceeds 10% of the ingested dose as presented in Equation A.15 when:

$$\text{For organics: } \frac{\text{Dermal}}{\text{Ingestion}} > 10\% \text{ when } (\text{FA}) (K_p) \sqrt{\tau_{\text{event}}} > 0.005 \quad (\text{A.16})$$

It should be noted that this screening procedure for exposure to water-borne chemicals is limited to the ingestion and showering pathways (using RME value for showering duration) for adults, and does not include consideration of swimming exposures, and therefore should not be used for screening chemicals in surface water where exposure may be through swimming activity. This procedure has also been evaluated to be more conservative than the scenario of children bathing for one hour (RME value for children bathing). In addition, site-specific scenarios and exposure conditions should always be used when available.

The screening criterion of 10% dermal exposure to ingestion exposure was selected to ensure that this screening procedure does not eliminate compounds of potential concern. This criterion introduces a safety factor of 10. For compounds with low GI absorption (e.g., < 50%), this screening procedure should not be used, and the actual GI absorption fraction should be used to adjust for the toxicity effect (see Section 3.2 on Dermal Absorption from Soil for methodology).

Exhibit B-3 in Appendix B lists more than 200 common organic pollutants and their permeability coefficients. The compounds are listed in alphabetical order. Assessors can check this list to see if the compound of interest is on the list. Chemicals which are considered appropriate to evaluate for the dermal pathway are indicated in Exhibit B-3 with a "Y" in the "Chemicals To Be Assessed" column. Exhibit B-4 provides the same information for all inorganics with a GI absorption fraction provided in Exhibit 4-1.

For inorganics, using the same procedure, the screening equation results in Equation A.17.

$$\text{For inorganics: } \frac{\text{Dermal}}{\text{Ingestion}} > 10\% \text{ when } K_p > ABS_{GI} \quad (A.17)$$

## A.5 PROCEDURES FOR CALCULATING DERMAL DOSE

This section presents the steps required to identify appropriate values for the exposure and absorption parameters, and notes how to combine these values to estimate the dermally absorbed dose of a compound in an aqueous medium.

### Step 1: Select Values for Exposure Parameters

Site-specific measurement or modeling is required to identify values for the concentration of the contaminant(s) of interest in water. Concentration values should be used that are representative of the location and time period where exposure occurs. Lacking site-specific data to the contrary, the default values presented in Exhibit A-9 are recommended for the parameters characterizing water contact during bathing.

Background information and the rationales supporting default recommendations are obtained from the Exposure Factors Handbook (U.S. EPA, 1997a), and are briefly summarized here. The exposed skin area is based on the assumption that people are entirely immersed during bathing or swimming; the corresponding body areas were presented in the Exposure Factors Handbook. The bathing frequency of 350 days/year is based on information that most people bathe once per day (1 event/day). The bathing event time is based on the range given in the Exposure Factors Handbook to be representative of baths as well as showers and considering that some water residue remains on the skin for a brief period after bathing. The exposure duration of 9 to 30 years

represents the likely time that a person spends in one residence, with 9 years used for central tendency residential exposure duration, and 30 years used for high end residential exposure duration.

## **EXHIBIT A-9**

### **DEFAULT VALUES FOR WATER CONTACT EXPOSURE PARAMETERS**

| Parameter                          | Bathing Default Parameters                   |
|------------------------------------|--|
| Adult Skin Area (cm <sup>2</sup> ) | 18,000                                       |
| Event Time and Frequency           | 35 min/event, 1 event/day<br>and 350 days/yr |
| Exposure Duration (years)          | 9 - 30                                       |

#### **Step 2:** Select Normalizing Parameters Used in Dose Equations

Dose estimates are normalized over body weight and time to express them in a manner that is consistent with dose-response relationships. An average body weight [70 kg for adults, see U.S. EPA, 1989 for age-specific values for children] is used for this purpose. For cancer risk assessments, an averaging time equal to a mean lifetime (70 yr) is used. For noncancer risk assessments, an averaging time equal to the exposure duration is used. (For more details regarding these parameters, see U.S. EPA, 1989.)

**Step 3:** Estimate  $DA_{\text{event}}$ 

These equations were given in Chapter 3 and Appendix A. Section A.1 gives the equations for the organics; Section A.2 gives the equations and values for inorganics. For organics:

### Dermal Absorbed Dose per event for Organic Compounds - Water Contact

$DA_{\text{event}}$  (mg/cm<sup>2</sup>-event) is calculated for organic compounds as follows :

$$\text{If } t_{\text{event}} \leq t^*, \text{ then: } DA_{\text{event}} = 2 FA \times K_p \times C_w \sqrt{\frac{6 \tau_{\text{event}} \times t_{\text{event}}}{1}} \quad (3.2)$$

$$\text{If } t_{\text{event}} > t^*, \text{ then: } DA_{\text{event}} = FA \times K_p \times C_w \left[ \frac{t_{\text{event}}}{1+B} + 2 \tau_{\text{event}} \left( \frac{1+3B+3B^2}{(1+B)^2} \right) \right] \quad (3.3)$$

where:

| <u>Parameter</u>    | <u>Definition (units)</u>  | <u>Default Value</u>                  |
|---------------------|--|---------------------------------------|
| $DA_{\text{event}}$ | = Absorbed dose per event (mg/cm <sup>2</sup> -event)  | --                                    |
| FA                  | = Fraction absorbed (dimensionless)  | Chemical-specific, See Appendix B     |
| $K_p$               | = Dermal permeability coefficient of compound in water (cm/hr)   | Chemical-specific, See Appendix B     |
| $C_w$               | = Chemical concentration in water (mg/cm <sup>3</sup> )  | Site-specific                         |
| $J_{\text{event}}$  | = Lag time per event (hr/event)  | Chemical-specific, See Appendix B     |
| $t_{\text{event}}$  | = Event duration (hr/event)  | See Exhibit 3-2                       |
| $t^*$               | = Time to reach steady-state (hr) = $2.4 J_{\text{event}}$   | Chemical-specific, See Eq. A.5 to A.8 |
| B                   | = Dimensionless ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis (ve) (dimensionless). | Chemical-specific, See Eq. A.1        |

Equations A.1 to A.8 update those in the *DEA* for estimating all parameters needed to evaluate  $DA_{event}$ :

$$B = \frac{K_p}{K_{p,ve}} = K_p \frac{\sqrt{MW}}{2.6} \text{ cm/hr} \quad (A.1)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>   | <u>Default Value</u>  |
|------------------|---|---|
| B                | = Dimensionless ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis (ve) | --  |
| $K_{p,ve}$       | = Steady-state permeability coefficient through the viable epidermis (ve) (cm/hr)   | $K_{p,ve} = K_{ew} D_e / L_e$ , $K_{ew} = 1$ assuming EPI behaves essentially as water; $L_e = 10^{-2}$ cm, $D_e = 7.1 \times 10^{-6} / MW \text{ cm}^2/\text{s}$ assuming $D_e = 10^{-6} \text{ cm}^2/\text{s}$ when $MW = 50$ (Bunge and Cleek, 1995) |
| $K_p$            | = Dermal permeability coefficient in water (cm/hr)  | Equation 3.8  |
| MW               | = Molecular weight (g/mole)   | Chemical-specific   |

Using the same approach as in *DEA*, Equation 5.13, A.2 and A.3 estimate  $D_{sc}/l_{sc}$  (cm/hr).

$$\log \frac{D_{sc}}{l_{sc}} = -2.80 - 0.0056 MW \quad (A.2)$$

or:

$$\frac{D_{sc}}{l_{sc}} = 10^{(-2.80 - 0.0056 MW)} \quad (A.3)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>   | <u>Default Value</u> |
|------------------|---|----------------------|
| $D_{sc}$         | = Effective diffusion coefficient for chemical transfer through the stratum corneum ( $\text{cm}^2/\text{hr}$ ) | Chemical-specific    |
| $l_{sc}$         | = Apparent thickness of stratum corneum (cm)  | $10^{-3}$            |
| MW               | = Molecular weight (g/mole)   | Chemical-specific    |

Assuming  $l_{sc} = 10^{-3}$  cm as a default value,  $\tau_{event}$  can be evaluated using Equation A.4:

$$\tau_{event} = \frac{l_{sc}^2}{6 D_{sc}} = 0.105 \times 10^{(0.0056 MW)} \quad (A.4)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>   | <u>Default Value</u> |
|------------------|---|----------------------|
| $J_{event}$      | = Lag time per event (hr/event)   | Chemical-specific    |
| $D_{sc}$         | = Effective diffusion coefficient for chemical transfer through the stratum corneum (cm <sup>2</sup> /hr) | Chemical-specific    |
| $l_{sc}$         | = Apparent thickness of stratum corneum (cm)  | $10^{-3}$            |
| MW               | = Molecular weight (g/mole)   | Chemical-specific    |

Calculate  $t^*$ :

$$\text{If } B \leq 0.6, \text{ then } t^* = 2.4 \tau_{\text{event}} \quad (\text{A.5})$$

$$\text{If } B > 0.6, \text{ then } t^* = (b - \sqrt{b^2 - c^2}) \frac{l_{\text{sc}}^2}{D_{\text{sc}}} \quad (\text{A.6})$$

where:

where:

$$b = \frac{2(1 + B)^2}{\pi} - c \quad (\text{A.7})$$

$$c = \frac{1 + 3B + 3B^2}{3(1 + B)} \quad (\text{A.8})$$

| Parameter          | Definition (units)   | Default Value     |
|--------------------|--|-------------------|
| B                  | = Dimensionless ratio of the permeability coefficient of a compound through the stratum corneum relative to its permeability coefficient across the viable epidermis (ve) (dimensionless). | Chemical-specific |
| $t^*$              | = Time to reach steady-state (hr)  | Chemical-specific |
| $J_{\text{event}}$ | = Lag time per event (hr/event)  | Chemical-specific |
| $D_{\text{sc}}$    | = Effective diffusion coefficient for chemical transfer through the stratum corneum ( $\text{cm}^2/\text{hr}$ )  | Chemical-specific |
| $l_{\text{sc}}$    | = Apparent thickness of stratum corneum (cm)   | $10^{-3}$         |
| b, c               | = Correlation coefficients which have been fitted to the Flynn's data to give Equation 3.8   | Chemical-specific |

For Inorganics:

### **Dermal Absorbed Dose per event for Inorganic Compounds - Water Contact**

$DA_{event}$  (mg/cm<sup>2</sup>-event) is calculated for inorganics or highly ionized organic chemicals as follows:

$$DA_{event} = K_p \times C_w \times t_{event} \quad (3.4)$$

where:

| <u>Parameter</u> | <u>Definition (units)</u>                                      | <u>Default Value</u>  |
|------------------|--|---|
| $DA_{event}$     | = Absorbed dose per event (mg/cm <sup>2</sup> -event)          | –   |
| $K_p$            | = Dermal permeability coefficient of compound in water (cm/hr) | Chemical-specific, see Exhibit A-6 and Appendix B                       |
| $C_w$            | = Chemical concentration in water (mg/cm <sup>3</sup> )        | Site-specific, non ionized fraction, see Appendix A for more discussion |
| $t_{event}$      | = Event duration (hr/event)                                    | See Exhibit 3-2   |

#### **Step 4: Integrate Information to Determine Dermal Dose**

Finally, the dermal dose is calculated by collecting the information from the earlier steps and substituting into Equation 3.1.

**Dermal Absorbed Dose - Water Contact**

$$DAD = \frac{DA_{event} \times EV \times ED \times EF \times SA}{BW \times AT} \quad (3.1)$$

where:

| <u>Parameter</u>    | <u>Definition (units)</u>                                    | <u>Default Value</u>   |
|---------------------|--|--|
| DAD                 | = Dermal Absorbed Dose (mg/kg-day)                           | –  |
| DA <sub>event</sub> | = Absorbed dose per event (mg/cm <sup>2</sup> -event)        | Chemical-specific, see Eq. 3.2 and 3.3   |
| SA                  | = Skin surface area available for contact (cm <sup>2</sup> ) | See Exhibit 3-2  |
| EV                  | = Event frequency (events/day)                               | See Exhibit 3-2  |
| EF                  | = Exposure frequency (days/year)                             | See Exhibit 3-2  |
| ED                  | = Exposure duration (years)                                  | See Exhibit 3-2  |
| BW                  | = Body weight (kg)   | 70 kg  |
| AT                  | = Averaging time (days)                                      | noncarcinogenic effects AT = ED x 365 d/yr<br>carcinogenic effects AT = 70 yr x 365 d/yr |

**Step 5: Further Refinement of Dose Estimate**

Where dose estimates are desired for children during specific age ranges, a summation approach is needed to reflect changes in skin surface area and body weight. Assuming all other exposure factors remain constant over time, Equation 3.1 is modified to Equation A.18; where m and n represent the age range of interest. The skin surface areas for the ages of interest can be obtained from Exhibit C-3 (Appendix C) and body weights from the Exposure Factors Handbook (U.S. EPA, 1997a).

**Dermal Absorbed Dose - Water Contact  
Surface Area/Body Weight Adjustment**

$$DAD = \frac{DA_{event} EF EF}{AT} \sum_{i=1}^n \frac{SA_i ED_i}{BW_i} \quad (A.18)$$

where:

| Parameter           | Definition (units)   | Default Value                              |
|---------------------|--|--|
| DAD                 | = Dermal Absorbed Dose (mg/kg-day)                           | --   |
| DA <sub>event</sub> | = Absorbed dose per event (mg/cm <sup>2</sup> -event)        | Chemical-specific, see Equation 3.12       |
| SA                  | = Skin surface area available for contact (cm <sup>2</sup> ) | See Appendix C and Equations 3.13-3.16     |
| EV                  | = Event frequency (events/day)                               | See Exhibit 3-5                            |
| EF                  | = Exposure frequency (days/year)                             | See Exhibit 3-5                            |
| ED                  | = Exposure duration (years)                                  | See Exhibit 3-5                            |
| BW                  | = Body weight (kg)   | EFH (U.S. EPA, 1997a)                      |
| AT                  | = Averaging time (days)                                      | noncarcinogenic effects AT = ED x 365 d/yr |

**Step 6: Screening**

$$\frac{\text{Dermal Dose}}{\text{Ingestion Dose}} = \frac{DA_{event}(SA)(EV)}{(C_w)(IR)(1000\text{cm}^3/\text{L})(ABS_{GI})} \quad (A.13)$$

where:

| Parameter           | Definition (units)  | Default Value   |
|---------------------|---|---|
| DA <sub>event</sub> | = Absorbed dose per event (mg/cm <sup>2</sup> -event)   | Chemical-specific, see Equation 3.12                                    |
| C <sub>w</sub>      | = Chemical concentration in water (mg/cm <sup>3</sup> )   | Site-specific, non ionized fraction, see Appendix A for more discussion |
| SA                  | = Skin surface area available for contact (cm <sup>2</sup> )  | See Appendix C and Equations 3.13-3.16                                  |
| EV                  | = Event frequency (events/day)  | See Exhibit 3-5   |
| IR                  | = Water ingestion rate (L/day)  |   |
| ABS <sub>GI</sub>   | = Fraction of contaminant absorbed in the gastrointestinal tract (dimensionless)<br>- For Organics: ABS <sub>GI</sub> is assumed to be 1 (or 100% absorption) |   |

## **Step 7: Evaluate Uncertainty**

As explained in Chapter 4 and Section A.4, the procedures for estimating the dermal dose from water contact are very new and should be approached with caution. One "reality check" that assessors should make for bathing scenarios is to compare the total amount of contaminant in the bathing water to the dose. The amount of contaminant in the water is easily computed by multiplying the contaminant concentration by the volume of water used (showers typically use 5 to 15 gal/min). Obviously, the dose cannot exceed the amount of contaminant in the water. In fact, it seems unlikely that a high percentage of the contaminant in the water could be dermally absorbed. As a preliminary guide, if the dermal dose estimate exceeds 50% of the contaminant in the water, the assessor should reexamine the assumptions and sources of data. Volatile compounds have been shown to volatilize significantly during showering. Andelman (1988) found that about 90% of TCE volatilized during showering. This would suggest that the effective concentration of volatile contaminants in water, and thus the resulting dermal dose for volatiles, may be reduced. So for volatile compounds, assessors may want to assume a reduced contaminant concentration in water contacting the skin.

The dermal permeability estimates are probably the most uncertain of the parameters in the dermal dose equation. As discussed in Section A.4, the measured values probably have an uncertainty of plus or minus a half order of magnitude. In addition, FA is obtained graphically to the nearest one significant figure, and therefore contributes somewhat to the uncertainty of the final calculation. Accordingly, the final dose and risk estimates should be considered highly uncertain. Some idea of the range of possible values can be obtained by first using average or typical values for each parameter to get a typical dose estimate. Setting two or three of the most variable parameters to their upper values and the others to their average values will also yield some idea of the possible upper-dose estimate.

### **A.5.1 STEPWISE PROCEDURE FOR CALCULATING DERMAL DOSE USING SPREADSHEETS**

Revised spreadsheets have been set up on LOTUS 123 to support the calculations for the dermally absorbed dose described in Chapter 2 and this Appendix for the organics (ORG04\_01.WK4) and the inorganics (INORG04\_01.WK4). These spreadsheets replace the previous ones sent to the Regions with the 1992 document. Electronic versions of the spreadsheets are provided on the Internet (<http://www.epa.gov/superfund/>

[programs/risk/ragse/index.htm](#)). The spreadsheets provide data for 209 organics and 19 inorganic chemicals, with all equations included. Calculations are also given for these chemicals, using either default or assumed values for the purpose of illustration.

Results from the spreadsheets for the organics are tabulated in Appendix B, Exhibits B-1 to B-3. For the organics, Equations A.1 to A.8 and 3.1 to 3.8 are set up for over 200 compounds in the spreadsheet. Given the log  $K_{ow}$  and MW of chemicals,  $K_p$  is estimated using Equation 3.8. Depending on the exposure duration ( $t_{event}$ ), either Equation 3.2 or 3.3 should be selected to be used in Equation 3.1. All other default exposure factors in Equation 3.1 are obtained from Chapter 3 and Appendix A.

Compounds from Exhibits B-2 and B-3 marked with an \* are the highly lipophilic compounds which are listed in Exhibit A-2. Compounds from the organics list marked with an \*\* are the halogenated compounds.

For each new site risk assessment, the following procedures need to be followed:

**Step 1:** Input parameter values common to all chemicals at the top of the spreadsheet, i.e. SA,  $t_{event}$ , EV, EF, ED, BW, AT. Default values for all these parameters can be found in Chapter 3 and in Appendix A.

**Step 2:** Compile the list of chemicals on the site and their concentrations.

**Step 3:** Find the chemicals on the spreadsheet provided. If not listed, find their Molecular Weight and Log  $K_{ow}$  and enter data for the new chemicals at the bottom of the spreadsheet. Copy the respective formulas for all the calculations to these new chemicals. Numerical values corresponding to the conditions on the site will be calculated automatically. Delete the ones not found on the site to obtain your own spreadsheet for the site.

**Step 4:** Enter the actual concentration of each chemical found on the site in the column marked "Conc".

**Step 5:** Check in the Column "Chemicals to be assessed" to find out whether or not you need to include that chemical in your Risk Assessment.

**Step 6:** Check on all Print setup for your particular printer. You can rearrange the columns to print only the values of interest by copying your spreadsheet to a new spreadsheet, pasting the values only, and not the formulas. This new spreadsheet can be formatted freely, as well as imported into a wordprocessing software as tables. Note that any changes in calculations still need to be done in the original spreadsheet with the embedded equations.